TEMPOROMANDIBULAR DISORDERS INTERAGENCY WORKING GROUP (TMDIWG) Research Agenda/Plan July 2000

I. Introduction

The National Institute of Dental and Craniofacial Research (NIDCR, formerly NIDR) is the component of the National Institutes of Health (NIH) that has been the primary sponsor for research on temporomandibular disorders (TMDs). TMDs are complex conditions involving pain and/or dysfunction of the temporomandibular joint (TMJ) and surrounding musculature. NIDCR has a long history of TMD research support, having awarded its first grant related to TMD in 1969, and has collaborated extensively with other NIH entities, as well as other agencies. The complexity of these disorders has involved research supported by numerous other NIH institutes and offices and has included work of relevance to other agencies of the Department of Health and Human Services (DHHS) and the Department of Defense.

House and Senate Appropriations Committee report language for NIDCR has for several years reflected continuing interest in research on the TMDs. FY 1998 language regarding TMDs for both Committees: (1) encouraged the Institute to "carry out the research recommendations of the Technology Assessment Conference on the Management of TMDs", (2) called on the NIDCR to form an "inter-institute committee along with representatives of the Office on Women's Health, AHCPR, and CDC to develop a short- and long-term research agenda;" and; (3) recommended a "study of TMJ patients who are suffering craniofacial and systemic problems as the result of implants." Similar language was included in the FY 1999 and FY 2000 Committee reports.

In response to this language, the NIDCR convened the TMD Interagency Working Group (TMDIWG) that held the first of a series of meetings in July 1998, developed and implemented a protocol evaluating patients with failed implants and continued support for TMD research and related activities. This plan reflects the status of the working group as of June 2000.

II. Background

The term "Temporomandibular Disorders" is used to describe a collection of clinical conditions that produce pain, discomfort, and limited mobility in the temporomandibular joint (TMJ) and associated facial musculature. These disorders are complex and on-going research continues to unveil the dimensions of their etiology and pathogenesis. There are a range of conditions that could potentially produce the pain and dysfunction associated with TMD that include primary conditions such as myofacial pain syndromes, as well as secondary conditions, including osteoarthritis of the temporomandibular joint or other degenerative conditions of this joint, facial trauma, or iatrogenic effects of surgery on or around the TMJ. Indeed, it is rapidly being appreciated that painful conditions of the facial masticatory musculature often extend to non-masticatory craniofacial muscles, and may often be part of a more global pain syndrome (fibromyalgia).

Epidemiological studies have begun to describe the magnitude of the problem. Up to 5% of the general population report clinically significant TMD-related pain and nearly 2% seeking treatment of a TMD symptom. Women report TMD-related symptoms about twice as frequently as men, and are much more likely to report the severity of symptoms. These differences are believed to reflect the increased use of heath services by women. In community-based studies, the differences between men and women diminish. TMDs appear to be a syndrome of young to middle aged adults, with a declining prevalence in the over 55 years old age group. Thus, TMDs do not appear to be a sign of deteriorating masticatory function, and TMD pain often disappears with advancing age.

The 1996 NIH Technology Assessment Conference on the Management of Temporomandibular Disorders (http://odp.od.nih.gov/consensus/ta/018/018_intro.htm) reviewed the evolution of potential etiological bases, clinical treatments for TMD, and the existing terminology and classification schemes. The conclusion was that the term TMD has been used to describe a wide variety of clinical conditions involving painful conditions in the jaw area, headaches, ear aches, abnormal occlusal wear, problems in joint mobility, clicking or popping sounds from the joint, as well as other complaints. There is a wide range in the clinical signs presented by these conditions, ranging from detectable but insignificant signs to seriously debilitating pain or dysfunction. Scientifically-based guidelines for the diagnosis and management of patients with TMD have not been formulated. While current research diagnostic criteria contain both physical and psychosocial axes that should be considered when evaluating and managing TMD pain, these criteria do not provide a potential physiological basis for the patient's problem. It is becoming increasingly clear that TMD symptoms are similar to those of other types of musculoskeletal disorders. Thus, a differential diagnosis between subtypes of TMD requires an understanding of the pathophysiology of musculoskeletal pain. Treatments for TMD have included a wide range of therapies, ranging from behavioral and physical therapy, occlusal splints, pharmacological treatments, to more invasive occlusal or

surgical procedures. While some patients appear to show improvement, many do not, and in some cases (alloplastic implants, multiple surgeries) patient outcomes have been catastrophic. The 1996 TMD Technology Assessment Conference concluded that there were a lack of data on the natural history of untreated TMDs, the effectiveness of current treatments, and the basis for specific interventions, in particular those involving invasive procedures.

III. The TMD Interagency Working Group—Purpose and Initial Activities and Meetings

The working group is comprised of representatives from four agencies in the DHHS. At the NIH, representatives come from the NIDCR, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), and the Office of Research on Women's Health. Other agencies represented include the Agency for Healthcare Research and Quality (AHRQ – formerly AHCPR), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). In addition, the working group includes representatives from patient advocacy groups, academia, and the Department of Defense

The TMDIWG facilitates cooperation, communication, and collaboration among agencies that conduct or support TMD-related activities. These activities may range from support for biomedical and behavioral research to direct provision of health care services. The TMDIWG provides both a forum for initiating interactions and a mechanism for tracking their progress. The group's activities began with the development and description of an inventory of DHHS TMD-related activities. TMDIWG meetings and projects currently tend to focus on bringing together in-depth information from the varied programs represented by the member organizations; being the catalyst for the initiation of projects; and guiding the progress of projects involving several agencies. A key function of the TMDIWG is to provide a forum for exchange and dissemination of information necessary to maintain effective coordination of DHHS activities related to TMDs.

Since its establishment in 1998, the TMDIWG has solicited broad input on current NIH and DHHS-related activities, constructed a draft framework around which a short and long-term research agenda addressing the many facets of these disorders can evolve, evaluated the current portfolio of activities and developed implementation plans.

In order to further progress with implementation of the TMD research agenda, the Working Group was broken down into 5 committees, each of which was co-chaired by TMDIWG members and that addressed a specific topic to enhance TMD research and training. The committees and their charges were as follows:

- **Basic Research Committee**: To explore crosscutting issues for collaboration among NIH ICs and between different component agencies of DHHS. To devise approaches for attracting new investigators (young as well as experienced ones from other areas of related science) into TMD research. To develop an initiative for expanding the basic research base on TMDs, to include a focus on etiology, pathogenesis and epidemiology of these disorders.
- **Implant Committee**: To explore opportunities for the development of more biocompatible implants. To explore the possibility of developing a patient registry of implant patients and/or TMD patients, and explore whether a medical alert for current TMD implant recipients is warranted.
- **Training Committee**: To review the current training and career development portfolio and develop outreach initiatives to expand the TMD research-training base.
- **Clinical Research Committee**: To develop initiatives to expand the clinical research on TMDs. Specific topics to be addressed include a re-examination of the research diagnostic criteria, with a goal to make them more physiologically-based; and to support studies of patient populations with symptoms analogous to TMD. To examine the feasibility of establishing a TMD Patient Registry. To develop a plan for enhancing the conduct of multi-center clinical trials to establish the efficacy of treatments currently in use.
- **Health Promotion and Public/Professional Outreach Committee**: To review and revise the available the NIDCR current material literature on TMDs and develop new tools. To assure that the scientific basis for current TMD treatments is accurately presented to both public and professional groups.

IV. Ongoing TMD Research

A. Basic Research

Several NIH Institutes and the FDA support basic research directly and indirectly related to the etiology, pathogenesis and epidemiology of temporomandibular disorders. The following represent examples, several which are the result of

previous NIH initiatives for research in the area of TMDs:

- Research includes the development of new models of peripheral orofacial pain due to experimental insults in and around the temporomandibular area, determining the neurotransmitters involved in transmitting the afferent signals to the central nervous system (CNS), and mapping the CNS regions to which these signals are received. The goal of many of these studies is to understand the effects of persistent pain of CNS plasticity, vis a vis the phenomenon of central hyperexcitability and behavioral hyperalgesia.
- Motor control of the TMJ in the presence of experimental TMJ pain in an animal model represents another area of active research. This includes studies of the central and peripheral nervous system, muscle activity, and jaw action.
- NINDS and NIDCR support research on the role of the trigeminal and opioid systems in pain transmission, peripheral and central factors contributing to hyperalgesia, and sex-mediated differences in pain perception. Examples of this include brainstem control of pain transmission, specifically how descending systems regulate the rostral transmission of noiciceptive information from the spinal cord; mechanisms in the development of neuropathic pain, including neuroimmune factors and the role of NMDA receptor antagonists; and CNS control of joint pain.
- Basic studies are investigating the effects of female hormones on the temporomandibular joint (TMJ). These hormones, specifically estrogen and relaxin, have one set of actions that “softens” and loosens the pelvic girdle of women during pregnancy (in order to ease delivery). Current work in an animal model seeks to determine if these hormones can promote systemic joint laxity and the development of disease in other joints, specifically the TMJ.
- NINDS, NIDCR, and the NINR support research on the apparent differences in pain sensitivity between women and men. Current projects support the development of animal model systems that might replicate this effect, and thus provide an approach to determining its’ mechanism of action. Evidence suggests that female mice have a sex-specific non-opioid analgesic mechanism; that male-female differences exist in opioid sensitivity (a finding replicated in recent clinical studies with specific opioid receptor agonists), and that specific genes or chromosomal regions may be responsible for these effects. Such evidence supports the possibility that the development of sex-specific analgesic approaches may be feasible in terms of drug development.
- Sex hormones appear to regulate masticatory muscle phenotype, expressed in terms of myosin isoforms, and oxidative and glycolytic enzyme content of muscle fibers. These muscle structure-function studies provide another basis for gender differences in TMJ structures. An important aspect to these studies is the effect that sex hormones may play in injury responses and regeneration.
- Investigators are focused on studying the anatomic and molecular biological features of neural pathways regulating the sensation of pain. Of particular interest are experiments on the molecular mechanisms involved in the development of physical dependence and tolerance to opioids, and on an endogenous substance that appears to guide nerve growth to appropriate targets during development. The latter experiments could shed light on mechanisms promoting nerve regeneration following injury.
- Investigators have uncovered new information on the molecular biology of pain transmission. For example, an experimental mouse model, with deletions of the gene encoding the neuropeptides Substance P and Neurokinin A, was found to have reduced pain responsiveness to intensely noxious stimulation, compared to little differences (compared to controls) when the stimulus was slightly greater than threshold. In addition, inflammatory processes mediated by neural mechanisms were almost completely abolished in this mouse model.
- Investigators have found that inflammatory mediators (endogenous chemicals released at the site of inflammation) appear to sensitive certain classes of central nervous system neurons (specifically, the trigemino-hypothalamic tract) that receive sensory information from craniofacial structures. This action provides a theoretical basis for the cutaneous allodynia (peripheral sensitivity to a usually non-noxious stimulus) found in patients during migraine attacks.
- The chemical conditions in the joint of patients with TMDs are conducive to free radical formation. Free radicals are a by-product of oxidative stress, and these substances could be contributing to damage of the articular tissues of the TMJ. The presence of by-products of free radical formation was correlated with subjective rankings of TMJ pain. The general concept of free radical damage as a precipitating or contributory factor to many disease states is rapidly gaining acceptance, and therapeutic agents that block free radical formation or that act as free radical scavengers are undergoing evaluation in clinical trials sponsored by other NIH Institutes.
- The NIDCR has recently funded projects designing approaches to enhance regeneration of orofacial muscle and bone, and the development of polymers to replace damaged cartilage.
- Finally, numerous studies on the effects of masticatory muscle contraction on facial bone mechanical stress and structural integrity, the effects of masticatory muscle function on TMJ function and extracellular tissue matrix structure, and the effects of jaw movement on CNS structures that regulate sensory feedback in normal oral function

are supported. Delineating the mechanics of the normal function of the craniofacial region may provide insights into pathophysiologic mechanisms involved in craniofacial dysfunction.

B. Clinical Research

Multiple institutes, including the NINDS, NINR, NIDCR and NIAMS have clinical pain portfolios that contain research related to conditions or syndromes that may be related to TMD.

For example, gender-based differences in TMD incidence is also reflected in gender-related differences in several other painful conditions such as irritable bowl syndrome, fibromyalgia. Other related conditions include Trigeminal Neuralgia and various forms of headache, as well as the development of hyperalgesia. In addition, the National Center for Complementary and Alternative Medicine (NCCAM) funds a center where complementary and alternative approaches to TMDs are under investigation.

- A series of clinical studies are evaluating the effects of gender, the menstrual cycle, female hormone levels, the CNS distribution of specific opioid receptor subtypes, and other gender-related factors, including pregnancy, on the appearance and severity of TMD. These studies could demonstrate relationships between generalized pain sensitivity, gender and hormonal status, and the development of TMD.
- NIDCR, NINDS, and NINR have projects looking at different aspects of gender-based differences in the response to opioid analgesia, as well as differences in opioid receptor subtypes that are present in women. Such differences are potentially clinically relevant, since many studies have shown that women show enhanced pain sensitivity compared to men. Current findings indicate that women have a greater ability to perceive heat pain (but not warmth) over a given period of time, compared to men.

There is a strong statistical relationship between the development of TMDs and other pain syndromes, especially fibromyalgia syndrome (FMS). Patients with FMS have chronic widespread pain, fatigue, sleep disturbances, and tender points. There is evidence that up to 2% of the population may suffer from FMS, with a much higher prevalence in women that increases with age. FMS appears to co-exist with other conditions, including TMDs and myofacial pain syndrome. NIDCR, NINDS, NIAMS, and NINR all sponsor research on the clinical manifestation and/or etiological basis for fibromyalgia.

- NIAMS has an extensive pain-related clinical research portfolio that deals with different aspects of fibromyalgia. The areas of research include studies of the central and peripheral nervous system, the hypothalamic-pituitary-adrenal axis, behavioral factors, the effects of exercise, and the effects of fibromyalgia on employment and family life.
- NIDCR-has recently funded several projects determining the relationship of TMDs with FMS and factors associated with the two conditions. One of the projects will examine these differences in an established, population-based multiracial female cohort, and assess racial differences regarding prevalence and the factors explaining this difference. The data collected thus far under the study offer a unique opportunity to study multiple risk factors thought to be associated with different types of chronic pain, as the study participants enter the most vulnerable period of life for developing such conditions.
- An on-going NIDCR clinical study/clinical trial is examining the relationship between four chronic pain syndromes: chronic fatigue syndrome, fibromyalgia, TMDs, and rheumatoid arthritis, including a comparison of different drug treatments. The goals are to first establish the interrelationship between adrenergic activity, neuroendocrine hormones, and cytokine function and then to assess the effects of adrenergic blockade. The goal of the drug trial is to assess the role the autonomic nervous system may play in influencing pain thresholds and tolerance.

Occlusal problems represent an established area of NIDCR-funded research addressing the problems of TMDs. The NIDCR has several TMD clinical trials recently completed or currently under way that address the problem of bruxism and its potential production of temporomandibular pain.

- A current clinical trial is examining the role of stress, distress, and bruxism in pain exacerbation in myofacial temporomandibular disorders. This trial will also compare the severity of bruxism in TMD patients and a control population, the contribution of bruxism to treatment outcomes, and the effectiveness of splints in TMD patients with bruxism.
- A recently funded clinical trial will study the efficacy of minimal treatment intervention in TMDs, using educational methods and innovative patient-centered materials. The long-term goal of this study is to develop safe and inexpensive self-management methods suitable for incorporation into dental practice. The use of oral appliances to address problems resulting from bruxism is included in this trial.
- There is preliminary evidence that TMD patients with myofacial pain and arthralgia symptoms engage in higher

levels of parafunctional activity compared to non-TMD controls. Replication of these levels of parafunctional activity seen in these TMD patients by normal controls produces symptoms consistent with a diagnosis of TMD. Current studies are testing the hypothesis that TMD patients engage in more episodes of parafunctional activity than matched controls, and that these types of behavior can produce the symptoms characteristic of myofacial TMD. The studies outlined in this proposal hold the promise of characterizing the role of parafunctional behavior in the etiology of some forms of TMDs, and could provide insights into effective intervention approaches.

Assessing factors that influence treatment decisions for patients with TMD is another aspect of research supported by the NIDCR. Research efforts are focusing on how health care professionals diagnose and treat this disorder, including the administration of pain medications.

- A series of educational interventions is being conducted among dentists and dental students to improve their knowledge and management of this disorder.
- An on-going randomized clinical trial to evaluate the role of psychosocial factors with regard to treatment decisions for TMD is underway. Treatment arms include minimal self-care intervention versus a course of cognitive-behavioral therapy. The hypothesis being tested is that complementing clinical TMD classification with biobehavioral classifications as the basis for treatment selection produces a better treatment outcome.
- Research on the Research Diagnostic Criteria classification system for TMDs, based on both physical symptoms and psychological factors is continuing. This clinical trial is attempting to validate this classification system, including measures of its clinical utility. Treating patients with a variety of pharmacological, behavioral and physical therapy treatments will test the latter aspect.
- A two-phase clinical trial is evaluating predictors of TMD progression and different biobehavioral treatments for chronic TMD. Phase I is currently evaluating the ability of the Research Diagnostic Criteria for TMD and the American Psychiatric Association DSM-III-R Axis I and Axis II diagnoses to be predictors of the progression from acute to chronic TMD problems. Phase II of the trial will test different behavioral treatments in those patients from phase I that have developed chronic TMD problems.

The health problems of patients who previously received a TMJ implant represent a potentially important area of research, since the development of medically safe TMJ prostheses is dependent on a thorough understanding of the previous problems that contributed to devise failure.

- The FDA Intramural Program is supporting research on immunogenetic risk factors associated with connective tissue and autoimmune diseases that develop in response to silicone containing medical devices.
- Investigators have performed a retrospective study of the self-reported immune-related health status of patients exposed to the Proplast-Teflon TMJ implant. Patients with the implant were compared to those who had the implant removed, as well as a group of TMJ patients without implants. The initial data analysis showed that implant-exposed patients did not differ in reported immune-related disorders compared to non-operated TMJ patients. Further analysis revealed that patients who had the implant removed were more likely to report systemic health problems than the group with retained implants. However, the number of immune system-related conditions was not significantly different between these two groups. One factor that did distinguish patients who had their implant removed from those with retained implants was an extremely low threshold for pain in those who had their implant removed.

The Intramural Program of the NIDCR is addressing selected aspects of clinical treatments for TMDs. Included in these efforts is a comprehensive evaluation of patients with failed TMJ implants that focuses on the local and systemic changes putatively associated with implants.

- Intramural scientists are nearing completion of a clinical study on patients with failed TMJ implants, and plan to publish their results in calendar year 2000.
- Several new clinical trial protocols evaluating treatments for TMDs were recently approved. The first protocol will compare the new anti-inflammatory drug Celebrex against a standard non-steroidal anti-inflammatory drug (Motrin). Since Celebrex has far less side effects than older drugs of this class, it may be an important therapeutic alternative. A second protocol is aimed at evaluating a new treatment for osteo- and rheumatoid arthritis (Embrel) in patients with advanced stages of TMD.

Finally, an NIH Technology Assessment Conference on “Improving Medical Implant Performance Through Retrieval Information” (Jan 10-12, 2000) was held. The recommendations of the non-Federal panel of experts suggest many steps that could be taken that would enhance the development of more biocompatible medical implants.

Conferences - Improving Medical Implant Performance Through Retrieval Information: Challenges and Opportunities

C. Health Services Research

Although there are many potential treatments that have been offered for TMDs, there are few, if any, randomized controlled clinical trials comparing different therapeutic modalities for these conditions. Problems in the diagnosis of the different subtypes of TMDs have contributed to the difficulties in performing clinical trials. A currently funded project is examining the elements used in the diagnosis and surgical management of TMJ surgery. In addition, the costs and consequences of surgical management will also be evaluated, using decision and cost-effectiveness analysis.

D. Research Capacity

There are several institutional research-training programs for oral health researchers that contain components relevant to TMD-related research. Specifically, these involve training in orofacial pain, somatosensory and motor function research. In addition a trans-NIH neuroscience training program that has relevance to TMD research. Finally, there are several individual training awards in orofacial pain research.

E. Health Education and Outreach

- **Education Materials:** In the early 1990s, NIDCR developed a patient education publication, **TMD: Temporomandibular Disorders**, which describes current thinking about the causes, signs and symptoms, diagnosis, and treatment of TMD. It cautions patients about treatments that may not be necessary as well as some that may actually be harmful. The booklet has been distributed through the National Oral Health Information Clearinghouse (NOHIC) since 1994. It was updated following the TMD Technology Assessment Conference in 1996.
- In response to the demand for information about TMD, the Clearinghouse also prepared an information packet on TMD for patients and healthcare professionals. The packet contains self-care tips for people with TMD, a resource organization list, selected articles on TMD, and a list of selected readings.
- **Inquiries and Information Dissemination**: From 1994-1999, NOHIC received 10,000 inquiries on TMD, and distributed 113,000 copies of the patient education booklet and 13,500 copies of the information packets.
- **Promotion of Education Materials:** NOHIC provided bulk quantities of the TMD booklet to TMD patient advocacy organizations for distribution through their networks. Supplies were replenished upon request.
- Sent press notice about availability of the TMD booklet to general, dental, and medical press.
- Conducted a multi-media effort to educate the public about TMD and the availability of the TMD booklet through North American Precis Syndicate, a national media relations firm. Targeted not only large media markets, but smaller ones as well, including weekly and community newspapers, radio, and TV.
- Promoted the TMD materials in a mailing to deans and department heads at medical, dental, and allied health professional schools and their libraries.
- Advertised the TMD booklet in the Vertical File Index, a resource for librarians nationwide.
- Featured the TMD booklet in the "Libraries as Gateways" program, a joint pilot project of Federal health information centers to help libraries become resources for consumer health information in their communities.
- Designed a "mini-display" for the TMD booklet for use at the NOHIC exhibit at major dental professional meetings.
- Wrote an article on TMD for special women's health issue of NIH News and Features, which is distributed to health reporters and editors.
- Put the TMD booklet online on NOHIC's web site.
- Provided the TMD booklet to the FDA Office of Consumer Affairs for their information packet on TMD.
- Provided the TMD booklet to the National Arthritis and Musculoskeletal and Skin Diseases Information Clearinghouse for their TMD information packet.

Finally, the NIDCR in 2000 developed a pictorial light box educational display on TMD for its entryway to the Institute on the NIH campus. All those coming to the Institute pass by this display.

V. Plan of Activities for TMDIWG

Research

- Goal: To stimulate interest of "new" investigators.
  1) Development of targeted presentations at scientific meetings, including:

- Neurosciences Society
- American College of Rheumatology
- American Pain Society
- Orthopaedics Research Society

2) Development and support of symposia
Participation and presentation at relevant NIH interest groups, such as:

- Pain Interest Group
- Human Brain Project

- Goal: To assess research opportunities and needs:
  1) Support of state-of-the science workshops:
     - Support was provided in FY 2000 for the First Annual Scientific Meeting of the TMJ Association (May 22-23, 2000) and the NIH Technology Assessment Conference on "Improving Medical Implant Performance Through Retrieval Information" (Jan 10-12, 2000).
  2) Systematic review of the literature
     - Plan to update the meta-analysis conducted in 1991-92.
  3) Exploration of health services research opportunities
     - The Health Care Financing Administration (HCFA) has little information available about the numbers or characteristics of beneficiaries who receive Medicare-covered services for TMDs. While the dental services provision of Medicare does not provide for TMD treatments, there may in fact be case-by-case coverage for "dental" TMD therapy. TMD treatment issues for Medicare coverage may meet a number of the conditions for which a review of national coverage policy may be warranted. Variability in coverage exists because Medicare has not issued definitive national policy regarding TMD therapy. For those concerned with public and private sector insurance coverage of TMD therapy, a national coverage review and policy decision by Medicare might be desirable because other health benefit programs often adopt Medicare policy. In order to affect a change from the current status quo, there needs to be sufficient clinical and scientific information about treatments that work, and those that do not. A strong research agenda will facilitate the development of the science base needed to proceed with appropriate treatment and Medicare coverage. HCFA may be willing to participate in clinical trials of TMD treatment interventions, with Medicare covering the treatments in the clinical trial setting.

- Goal: To coordinate and manage the TMD-related research portfolio among TMDIWG members
  - Ongoing activities to be assessed annually.

- Goal: To develop and support for research initiatives
  - A Program Announcement was developed and presented to the NIDCR Advisory Council for review. This initiative proposes the solicitation of innovative basic research proposals to study the pathogenesis of orofacial pain, in particular temporomandibular disorders. A broad range of research proposals including exploration of paththogenic mechanisms, new animal models, and interventions to halt and reverse disease processes among others will be encouraged.
    This initiative also is intended to solicit both design and hypothesis-driven applications whose aim is to develop novel bioengineering approaches for controlled site-directed delivery systems and synthetic biodegradable polymeric scaffolds for repair and regeneration of the different components of the temporomandibular joint and development of imaging technologies for the orofacial region. Even though bioengineering has provided successful therapeutic solutions for the restoration/regeneration of many tissues and organ, TMJ implants/prostheses have failed necessitating the development of novel materials for TMJ structure repair. The coupling of advances in the knowledge of the physiology, molecular biology and pathology of the TMJs, with improvements in the characterization and rational synthesis of biomaterials, may make possible an integrated/multidisciplinary research approach for the design and development of novel synthetic materials that are compatible with the environment of the host.
  - Plans are underway to develop a clinical trials initiative that would address efficacy of various TMD treatments.
  - Steps have been taken to involve the international research community in TMD research.

Research Training and Career Development

The NIDCR Office of Training and Career Development is planning a series of "Train the Trainer" seminars for health professions schools with a focus on dental students around the United States. These will provide an update on the findings of the 1996 NIH Technology Assessment Conference on the Management of Temporomandibular Disorders.

Health Education and Outreach

Future activities include updating the current NIDCR TMD booklet and information pack, broadening the distribution to include HMOs, contracting with a public relations firm to publicize the availability of these resources, and the more rapid publicizing of scientific findings with clinical implications. A more standardized patient referral program for patient inquiries that come to NIDCR staff will be developed.

VI. Timetables and Assessments

1. TMD Program Announcement: FY2001 publication date in the NIH Guide.
2. Development of a tracking plan for investigators responding to the proposed TMD PA or others developed by members of the Working group. This will allow the Working Group to identify those who either have not worked in the area of TMDs or who are expanding their research efforts into areas of the problem they have previously not addressed.
3. Future Working Group Meetings: Two meetings a year are proposed. A meeting in December will be used to review the progress from the previous fiscal year, while a meeting in June will be used for information exchange from all the subgroups.

NIDCR Intramural Clinical Trials (currently recruiting individuals)

The site for information on NIH clinical trials is http://clinicalstudies.info.nih.gov/index.html.

The Role of Cytokines as Inflammatory Mediators in Painful Temporomandibular Joints

Summary: This 2-part study will evaluate the effectiveness and side effects of two anti-inflammatory drugs for relieving pain and improving jaw function in patients with temporomandibular disorder (TMD). Part 1 will evaluate celecoxib (Celebrex); Part 2 will evaluate etanercept (Enbrel). The Food and Drug Administration has approved both of these drugs for treating certain forms of arthritis.
http://clinicalstudies.info.nih.gov/cgi/wais/bold011999.pl?/u/protocols/clinical_studies/html/internal_detail/A_2000-D-0037.html@tmd

Patient Evaluation and Treatment of Oral Soft Tissue Diseases According to Generally Available, Standard Procedures and Therapeutic Modalities

Summary: The function of this protocol is to support the training of residents in Oral Medicine, in the management of oral soft tissue diseases. Patients enrolled in this protocol will be evaluated and treated according to available standard procedures and therapeutic modalities. Samples of blood and oral tissues will be studied by routine and specialized investigative methods to establish the diagnoses, responses to treatment, and/or disease progression.
http://clinicalstudies.info.nih.gov/cgi/wais/bold011999.pl?/u/protocols/clinical_studies/html/internal_detail/A_1997-D-0169.html@tmd

A Phase I Trial of Brief Intravenous Infusion of the AMPA Receptor Blocker LY293558 to Examine Safety and Effects on Pain Perception in Normal Volunteers

Summary: The available therapies to treat neuropathic pain (such as opioid, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants) are at best only partly effective. During the past 10 to 15 years, there has been a growing body of evidence suggesting that chronic pain due to nerve or soft tissue injury may result in the sensitization of the central nervous system, and are modulated by the excitatory amino acids, glutamate and aspartate. The development of compounds which both excite and block the three classes of receptors to which the excitatory amino acids bind (NMDA, AMPA, and kainate receptors) has led to a new body of data which suggest that a new therapeutic approach is to directly block excitation. There is accumulating data supporting the role of AMPA receptor stimulation in processing pain. Normal volunteers will be administered escalating doses of the AMPA receptor blocker LY293558, given as a 15 minute infusion. This trial will (1) determine the toxicity associated with the maximally tolerated dose of this drug in normal subjects, (2) assess the effect of AMPA receptor blockade on normal pain perception, and (3) determine the efficacy on the intense pain evoked by intradermal capsaicin.
http://clinicalstudies.info.nih.gov/cgi/wais/bold011999.pl?/u/protocols/clinical_studies/html/internal_detail/A_1996-D-0119.html@chronic

Somatosensory Studies of Pain and Pain Control Measured with Oxygen-15 Water Positron Emission Tomography and Functional MRI in Normals and Patients with Neuropathic or Chronic Pain Conditions

Summary: Regional cerebral blood flow (rCBF) will be measured while normal subjects, patients with post-operative pain, and

patients with neuropathic abnormalities of pain sensation are exposed to a battery of somatosensory stimuli that activate known pathways subserving touch, temperature and pain sensations. Patients with peripheral neuropathies and other chronic pain conditions that cause spontaneous pain, hyperalgesia, and allodynia (pain sensation to a normally non-noxious stimulus) will be examined with and without applied experimental stimuli. Data from the patient groups will be compared to those of normal controls. In addition, an ultrashort opioid analgesic will be administered to normally and select patients in order to map opioid modifications of pain neural activity. Activation of several somatosensory modality in conjunction with high resolution positron emission tomography (PET), adjunctive structural imaging with magnetic resonance imaging (MR.) and analgesic drug manipulations will functionally, anatomically, and pharmacologically characterize the physiology and pathophysiology of nociceptive in human beings.
http://clinicalstudies.info.nih.gov/cgi/wais/bold011999.pl?/u/protocols/clinical_studies/html/internal_detail/A_1992-D-0243.html@chronic